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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GUIDRY, GUY L	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 06/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/026,331	HITOSHI ET AL.	
	Examiner	Art Unit	
	Guy Guidry, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-41,53 and 54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-41,53 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/21/2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a response filed 25 January to the Office Action mailed 21 October 2005. Claims 8-41 and 53-54 are currently pending in this application. Claims 8 and 41 have been amended. Claims 8-41 and 53-54 are under consideration in this Action. All objections/rejections not repeated herein are hereby withdrawn. A response to Applicant's arguments will be set forth, where appropriate, immediately following any statement of rejection repeated herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-41 and 54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Response to Applicant's amendments and arguments

Applicants have amended claims 8 and 41 so that the MRE11 polypeptide has at least 95% amino acid sequence identity to SEQ ID NO: 2 and therefore the scope of the claimed inventions utilizes a genus of MRE11 polypeptides having both structural and functional correlation.

The claims are drawn to MRE11 polypeptides and MRE11-encoding polynucleotides having at least 95% amino acid sequence identity to SEQ ID NO: 2 (claim 8-41) and SEQ ID NO: 1 (new claim 54) respectively.

The number of possible nucleotide sequences that are of a given % identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following formula:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + \ldots + X^{n-1}L(L-1)(L-2)\ldots(L-(n-2))/(n-1)! + X^nL(L-1)(L-2)\ldots(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence, L is the length of the reference sequence, n is the maximum number of residues that can be substituted relative to the reference sequence at a given % identity. For a nucleotide sequence, X is 3 (alternate nucleotides); for an amino acid sequence, X is 19 (alternate amino acids). The first term gives the number with one substitution, the second with two substitutions and so on to the number with n substitutions. The last term can be simplified for calculation to: $X^n L! / n! (L-n-1)!$

Thus, for SEQ ID NO : 2 containing 708 residues, with 19 alternate amino acids and 34 (5% of 708 residues or 95%identity) residues that can be substituted relative to the reference, the number of possible variants is 19^{34} 708 !/34 !(708-34-1) !., an astonishingly large number of potential sequences that would require copious experimentaion for a person of ordinary skill in the art to make and particularly to use in

determining which sequences have the recited functionality of nuclease activity. The number of claimed potential embodiments of SEQ ID NO : 2, comprising 2537 residues, is even considerably larger number of polynucleotides.

Thus, claims are directed to tremendously large number of structures that must correlate to the functionality of encoding an MRE11 protein. In other words, the claims encompass a very large genus of polypeptide and nucleic acid structures that encode an MRE11 protein thus necessarily encode a protein with MRE11 functionality.

In the context of the instant claims, the critical or essential elements are at minimum the minimal or conserved nucleic acid sequences (i.e., structures) that correlate to any MRE11 functionality The only disclosed embodiment is that of SEQ ID NO: 1. No additional structures are identified nor is additional evidence presented in the specification that clarifies or identifies what particular sequences or regions within SEQ ID NO: 1 are conserved or necessary so as to correlated to MRE11 functionality. In fact, the number of potential species encompassed by the claimed genus is further amplified insofar as the claims are directed to any functionality that is ascribed to MRE11 whether indirectly or directly. (e.g., Specification, ¶ 0056; note: all references to the specification correspond to the published version of this application, i.e., USPG. PUB. NO. 2003/0027167). Given that the instant disclosure provides a single example for such a tremendously large genus of structures, there is a notable gap in the specification regarding description of sufficient or representative number of embodiments.

However, there does not appear to be any evidence in the art to demonstrate the identity of particular conserved sequences that correspond to a given function. Furthermore, there does not appear to be any evidence to suggest that there is a representative structure common to all MRE11 proteins across any species of organism, whereby said structure correlates to any one of the preceding multiple functions ascribed to MRE11. Moreover, because many of MRE11 functions are not ascribed to MRE11 alone, but rather, MRE11 functioning in a complex of proteins (e.g., complex with RAD50 and XRS2 proteins), then the description must necessarily take into account that portions of MRE11 that are necessary for protein-protein binding would also have to be clarified (e.g., through mutational or deletion analysis). (e.g., Paull et al. Genes Dev. 1999; 13:1276-88; teaching that the Mre11/Rad50/Nbs1 complex displays several distinct enzymatic activity that are not observed without Nbs1; this reference is of record). In other words, in the context of the instant claimed methods, the necessary and critical elements would regarding independent claims 8 and 41 include nucleic acids that not only encode a functional motif but also a motif that is necessary and sufficient to bind partner proteins so as to form the necessary complex in the first place.

In sum, given the very limited disclosure of a single species, given the large breadth of the structures necessary to practice the, and encompassed by, the rejected claims, and the skilled artisan would not have been able to envision a sufficient number of specific embodiments to described the broadly claimed genus of polypeptides polynucleotides having at least 95% amino acid sequence identity to SEQ ID NO: 2 (claim 8-41) and SEQ ID NO: 1 (new claim 54).

Moreover, an applicant claiming a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from other species. Therefore, the skilled artisan would reasonably have concluded that applicants were not in possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 8-12, 14-17, 19, 23-30, 34-36 and 38-41, 53 and 54 are rejected under 35 U.S.C. 102(e) as being anticipated by Morris et al. (US 2002/0182586), hereinafter Morris.

Response to Applicant's amendments and arguments

Applicants have amended the claims to incorporate the language of step (iii) from claim 41 as step (iii) in claim 8. Applicants argue that this element was not disclosed by Morris. The claims are interpreted consonant with the interpretations detailed in the October 2005 Office Action.

Applicants' arguments have been fully considered but they are not persuasive. Applicant's essential argument is that Morris does not teach step (iii) of claims 8 and 41:

(iii) determining the chemical or phenotypic effect of the compound upon a cell comprising an MRE11 polypeptide, thereby identifying a compound that modulates cellular proliferation or chemosensitivity.

This rejection is of record; relevant portion of the previous rejection germane the instant rejection are presented here in modified form. Morris teaches a method of screening drug candidates comprising providing a cell that expresses a carcinoma associate (CA) gene and screening for compounds that inhibit cell proliferation. Specifically Morris provides:

"In accordance with the objects outlined above, the present invention provides methods for screening for compositions which modulate carcinomas, especially lymphoma and leukemia. Also provided herein are methods of inhibiting proliferation of a cell, preferably a lymphoma cell. Methods of treatment of carcinomas, including diagnosis, are also provided herein"(¶0007).

"In one aspect, a method of screening drug candidates comprises providing a cell that expresses a carcinoma associated (CA) gene or fragments thereof (¶0008).

As detailed in the 21 October 2005 Action, SEQ ID NO: 1224 disclosed in Morris and instant SEQ ID NO: 2 (MRE11 polypeptide) are 100% identical. Thus, Morris discloses a polypeptide identical to instant claims MRE11 polypeptide (claim 53) and also a polypeptide with 95% amino acid sequence identity to SEQ ID NO: 2 of part (i) of claims 8 and 41. Thus, the Morris cell is necessarily equivalent to the cell comprising an

MRE11 polypeptide of step (iii) of instant claim 8 and 41 (see the October 2005 Action for a full analysis of sequence comparison between the Morris and instant claimed sequences). Further, as detailed in the October Action, Morris teaches that CAPs can be encoded by the nucleic acid sequences as depicted in Table 1, which discloses SEQ ID NO: 1223, whereby said sequence shares over 97% identity with instant SEQ ID NO: 1, meeting the limitations of the nucleic acid sequence of new claim 54.

The methods taught by Morris include screening bioactive agents capable of binding to a CA protein (CAP, or SEQ ID NO: 1223) (e.g., ¶ 0010). Morris teaches identification of bioactive agents capable of modulating CA protein activity by adding a candidate agent to a cell comprising CA proteins (¶0193) to identify compounds with pharmacological activity that are able to enhance or interfere with the activity of CA protein (¶0195). Such methods encompass methods of identifying of bioactive agents such as a carcinoma cancer inhibitor inhibiting carcinoma cell division (¶0196) and lymphoma carcinoma cancer inhibitor inhibiting lymphoma carcinoma cell division (¶0197), thus meeting the limitation of the first part of claims 8 and 41step (iii) determining the chemical or phenotypic effect of the compound upon a cell comprising MRE11. Further, the method of screening embraces screening for agents capable of modulating the activity of a CAP, including activity of compounds as they affect *cell proliferation* (e.g., ¶ 0011, and see especially ¶0191) wherein the screening encompasses *in vivo* screening of cells (bottom of ¶0190), meeting the limitation of the second half of instant step (iii), identifying a compound that modulates cellular proliferation.

With respect to the limitation wherein the polypeptide of step (i) of claims 8 and 41 has at least 95% sequence identity to SEQ ID NO: 2 and has nuclease activity, it is assumed that since the polypeptide disclosed by Morris as SEQ ID NO: 1223 is identical to instant SEQ ID NO: 2, and SEQ ID NO: 2 has nuclease activity then the Morris polypeptide also has nuclease activity. The Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2 d 1922, 1923 (BPAI 1989).

Conclusion

No claims are allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Guy Guidry, Ph.D. whose telephone number is 571-272-7928. The examiner can normally be reached on Monday through Friday 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) (http://pair-direct.uspto.gov) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Guy Guidry, Ph.D.

Examiner

Art Unit 1636

DANIEL M. SULLIVAN
PATENT EXAMINER